DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

M3833n

VIA FEDERAL EXPRESS

MAY 8 2000

WARNING LETTER

Mr. Joseph S. Gallagher
General Manager and Director
Biosil Limited
127 Deerdykes View
Westfield Industrial Estate
Cumbernauld, G68 9HN
Glasgow, Scotland

Dear Mr. Gallagher:

During an inspection of your firm located in Glasgow, Scotland on April 17 through April 20, 2000, our investigator determined that your firm manufactures saline fill mammary implants. These are devices as defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Devices Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as listed below.

1. Failure to establish and maintain procedures for implementing corrective and preventive action including requirements for analyzing processes, work operations, quality records, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems, and identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(1) and (3). For example:

   a. Application for Concession/Process Variation Permit No. [redacted] has not been closed out, and it is not clear whether an investigation of the problem, bubbles visible on shells, was performed or completed.

   b. Nonconformance Report No. [redacted] identifies a nonconformance on uncured patches of metal visible on the shell, which appear to be excessive bubbling, but are also tacky. Although the report is signed off as closed out, it is not clear from the history sheet whether a final determination was reached that will correct the problem and prevent it from recurring.

2. Failure to, where the results of a process cannot be fully verified by subsequent inspection and test, validate the process with a high degree of assurance and approve the process according to established procedures, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented, as required by 21 CFR 820.75(a). For example:

   a. The validation of the new curing oven used in the manufacture of saline fill mammary implants is incomplete in that the validation was started [redacted] under Process Variation Permit [redacted] and is ongoing, and two additional Process Variation Permits (# [redacted] dated [redacted] and # [redacted] dated [redacted] have been issued for this validation since it was initiated.

   b. The validation of the Machine Washing and Drying of the Room Temperature Vulcanization (RTV) shells is [redacted] incomplete in that the type and capabilities of washing machine are not listed.

3. Failure to establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met, as required by 21 CFR 820.75(b). For example, the parameters for the length of the cycle and the temperature of the water are not specified.

4. Failure to establish and maintain procedures for finished device acceptance to ensure each production run, lot, or batch of finished devices meets acceptance criteria, and holding the finished devices in quarantine without releasing them for distribution until the activities required in the device master record are completed, and the associated data and documentation is reviewed, as required by 21 CFR 820.80(d). For example, Process Variation Permit # [redacted] dated [redacted] states the reason for the application is "to allow shells manufactured in the new curing ovens to be used in production until validation completion". The Process Variation Permit [redacted] is not signed off as being completed by the General Manager, and validation of the new curing ovens is not completed.

5. Failure to, where process controls are needed, include documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production, as required by 21 CFR 820.70(a)(1). For example, Process Variance [redacted] dated [redacted] specifies the shells be washed inside out because the shells and patches were failing the fusion joint test. The validation of

November 1998 does not state if the RTV shells were washed and dried inside out. The procedure "Training Instruction Stripping Shells [redacted] states under section 4.17 to leave all shells inside out before machine washing in section 4.20. In another procedure "Training Instruction IPA and Hot Water Wash [redacted] section [redacted] states to turn all RTV shells inside out.

6. Failure to, where environmental conditions could reasonably be expected to have an adverse effect on product quality, establish and maintain procedures to adequately control these environmental conditions, as required by 21 CFR 820.70(c). For example, the temperature and humidity in the clean room are not specified. However, they are monitored.

   The Annual Validation Testing states the temperature fluctuated, but in general the temperature was around with [redacted] humidity. Technical Dossier No. [redacted] notes that the dipping process is to be carried out at a humidity of less than

7. Failure to establish and maintain procedures for changes to a specification, method, process, or procedure that shall be verified or, where appropriate, validated according to Sec. 820.75 before implementation and these activities shall be documented and approved in accordance with Sec. 820.40, as required by 21 CFR 820.70(b). For example:

   a. A Dispersion Mixing Record No. [redacted] has a handwritten cross-out changing [redacted] to [redacted]

   b. A posted unsigned Process Development Memo dated 10/29/99 specifies a new chart recorder setting for the [redacted] Oven.

8. Failure to establish and maintain procedures to control all documents that are required including designating an individual(s) to review for adequacy and approve prior to issuance all documents established to meet the requirements of this part, including the date and signature of the individual(s) approving the document, and making all documents available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents promptly removed from all points of use or otherwise prevented from unintended use, as required by 21 CFR 820.40(a). For example:

   a. The validation protocol for the new curing oven has not been approved and dated by designated individuals.

b. A Microbiology Monitoring Regime for the [redacted] facility remains in the manufacturing area of the Cumbernauld facility.

9. Failure to review and approve by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise, changes to documents, including a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective, as required by 21 CFR 820.40(b). For example:

a. Dispersion Mixing Record No. [redacted] is changed with a handwritten cross-out changing [redacted] to [redacted].

b. A posted unsigned Process Development Memo dated 10/29/99 identifies a new chart recorder setting for the [redacted] Oven.

10. Failure to establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product including the justification for use of nonconforming product and the signature of the individual(s) authorizing use, as required by 21 CFR 820.90(b)(1). For example, Process Variation Permit [redacted] dated [redacted] gives the reason for the application as "to allow shells manufactured in the new curing ovens to be used in production until validation completion". The variance is not signed off as completed, and is not signed by the General Manager.

11. Failure to maintain device master records (DMR's) for each type of device including or referring to the location of production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications, as required by 21 CFR 820.181(b). For example:

a. The parameters for the length of the machine washing and drying cycle and the temperature of the water are not specified.

b. Although the validation does not state if the RTV shells were washed inside out, Process Variation Permit [redacted] dated [redacted], specifies the shells be washed inside out.

c. There is no specification or production method specifying the temperature and humidity in the clean room, however, the temperature and humidity are monitored.

12. Failure to maintain device master records (DMR's) for each type of device including or referring to the location of device specifications, including appropriate drawings, composition, formulation, component specifications, and software specifications, as required by 21 CFR 820.181(a). For example:

    a. There are no formalized specifications for the Class "J" clean room. The floor plan drawing attached to the Environmental Monitoring procedure [redacted] dated [redacted] is not approved or dated, and does not reflect the location of the equipment in the clean room; the sketches in the Microbiology manual are not signed and dated as approved, and the floor plans on pages 49-50 in that same manual differ from the validation contractors floor plan.

    b. There are no approved component specifications for the High Strength RTV Silicone Elastomer, specification number [redacted] Raw material specifications consist of a folder containing the vendors Technical Bulletins referencing the vendors P/N [redacted] several of the vendors Technical Bulletins for Medical Grade RTV Silicone Elastomer Dispersion in [redacted] additional vendor bulletins, and FAX's between the firm and vendor.

13. Failure to establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services, as required by 21 CFR 820.50(b). For example, there is no data maintained identifying the specifications for raw material components provided by the supplier. The only documentation available is memoranda and FAX's between Biosil and the supplier discussing only proposed specifications.

14. Failure to inspect, test, or otherwise verify as conforming to specified required incoming product, and documenting acceptance or rejection, as required by 21 CFR 820.80(b). For example, there are no inspections or tests performed on incoming product. The Technical Bulletin documentation provided by the supplier is placed in a folder for each product as confirmation the product meets the supplier's requirements.

15. Failure to establish and maintain procedures for acceptance activities, including inspections, tests, or other verification activities, as required by 21 CFR 820.80(a). For example, there are no procedures for acceptance activities, nor any acceptance activities performed on receipt of components. The only activity is to receive the

component, the supplier's document verifying the status of the component, and to file the supplier's document.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the form FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the Food and Drug Administration. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

In order to facilitate FDA in making the determination that such corrections have been made and thereby enabling FDA to withdraw its advisory to other federal agencies concerning the issuance of government contracts, we are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that s/he has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the GMP requirements of the Quality System Regulation (21 CFR, Part 820). You should also submit a copy of the consultant's report, and certification by your firm's Chief Executive Officer (CEO) (if other than yourself) that your firm has initiated or completed all corrections called for in the report. The attached guidance may be helpful in selecting an appropriate consultant.

The certification of audits should be submitted to this office by the following date:

- Initial certification by an outside consultant no later than [redacted]

Given the serious nature of these violations of the Act, all devices manufactured by Biosil Limited, 127 Deerdykes View, Westfield Industrial Estate, Cumbernauld, G68 9HN, Glasgow, Scotland may be detained without physical examination upon entry into the United States (U.S.) until these violations are corrected.

In order to remove the devices from detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review, and have an outside consultant certify your compliance with the Quality System Regulation no later than November 15, 2000. After we notify you that your response is adequate, it will be necessary to schedule an inspection of your facility. Our Division of Emergency and Investigational Operations will contact your facility about

scheduling the inspection. As soon as the inspection has taken place, and the implementation of your corrections has been verified, your products may resume entry into this country.

Please notify this office in writing of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. Please include any and all documentation to show that adequate correction has been achieved. In the case of future corrections, an estimated date of completion, and documentation showing plans for correction, should be included with your response to this letter.

If documentation is not in English, please provide an English translation to facilitate our review.

Your response should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement I, General Surgery Devices Branch, 2098 Gaither Road, Rockville, Maryland 20850, to the attention of Carol Shirk.

Sincerely yours,

for/ Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

[redacted]